REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Applicants respectfully submit that prior to the present amendment, Claims 28-40 were pending in this application and were rejected on various grounds. With this amendment, Claims 36 and 37 have been canceled without prejudice. The rejection of the remaining claims is respectfully traversed.

Claims 28-35 and 38-40 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. Amendments to Claims 28-32 can be found at least in Example 143 starting on page 494, line 20 of the specification.

Applicants thank the Examiner for entering the amendments of December 11, 2001 and August 29, 2002.

1. Information Disclosure Statement

In response to the Examiner's assertion on page 2 of the Office action that references 12 and 13 in the Information Disclosure Statement filed on October 10, 2002 are not in proper format, Applicants file herewith, an Information Disclosure Statement listing each reference of the "Blast Search" separately and including authors/inventors, relevant accession numbers and publication dates. Applicants respectfully request that the listed information be considered by the Examiner and be made of record in the above-identified application.

2. Specification

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code. In addition, the title of the application has been amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

Priority

As discussed below, Applicants rely on the gene amplification assay (Example 143) for patentable utility which was first disclosed in U.S. Provisional Application No. 60/162,506, filed October 29, 1999, priority to which has been claimed in this application.

As will be shown, the disclosure of the instant application, which is similar to that of the earlier-filed application (see Example 20, Provisional Application No. 60/162,506), provides the support required to establish utility for the claimed protein, for example, in detecting over-expression or absence of expression of the PRO1788 polypeptide. Accordingly, Applicants submit that the subject matter of the instant claims is supported by the disclosure in U.S. Provisional Application No. 60/162,506. Therefore, the effective filing date of this application is October 29, 1999, the filing date of U.S. Provisional Application No. 60/162,506.

3. Claim Rejections Under 35 U.S.C. § 101

Claims 28-40 are rejected under 35 U.S.C. 101 allegedly "because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility." The examiner alleges:

> The sole assay disclosed within the specification is that PRO 1788 tested positive in the gene amplification assay (Example 143, pgs. 494-503 & 506). This information may provide a credible, specific and substantial utility for PRO1788 nucleic acids, but not for PRO1788 polypeptides or antibodies. In other words, the preliminary data in the specification were not supported by analysis of mRNA or protein expression. Accordingly, the literature reports that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression, such that the claimed polypeptides would be useful for diagnosis of cancer or as a drug target ...

The Examiner further asserts that "even if gene amplification did correlate with increased transcription in a particular situation, it does not always follow that protein levels are also amplified" citing Haynes *et al* (1998).

Applicants respectfully disagree and traverse the rejections. Applicants submit that the cancellation of Claim 36-37 renders the rejection of these claims moot. Claims 28-35 and 38-40 have patentable utility for the reasons discussed below.

Legal Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is *a preponderance of the totality of the evidence* under consideration. *In re* Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that ***it is more likely than not*** that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the

"substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a "substantial" utility." M.P.E.P. 2107.01, emphasis added. Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." M.P.E.P. 2107 II(B)(1)(ii). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Revised Interim Utility Guidelines Training Materials, 1999.

Proper Application of the Legal Standard

Applicants submit that the invention defined by the presently amended claims has specific, substantial and credible utility for the claimed polypeptides.

As discussed above, Applicants rely on the gene amplification data for priority and to establish patentable utility for the PRO1788 polypeptide. This data was first disclosed in Provisional Application No. 60/162,506 filed on October 29, 1999, the priority of which is claimed in the present application. Hence, the effective filing date of the present application is October 29, 1999 for subject matter of the instant claims defined in Claims 28-35 and 38-40.

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 143 of the present application, the inventors

isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 8 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc.

The specification discloses that the nucleic acids encoding PRO1788 had ΔCt value of > 1.0, which is **more than 2 -fold increase**, for primary colon tumors: CT1, CT3, CT4, CT8, CT9, CT10, CT12, and CT14. Because amplification of DNA77652-2505 (PRO1788) occurs in various colon tumors, it is highly probable to play a significant role in tumor formation or growth, and antagonists (e.g. antibodies) directed against the protein encoded by DNA77652-2505 (PRO1788) would be expected to have utility in cancer therapy.

It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts

disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1788 is ***a diagnostic marker of colon cancer.***

Regarding the Examiner's point that "the specification has assigned no specific activity to PRO1788" and the "asserted utilities are further not "substantial" (see page 5 of the Office Action), Applicants submit, as discussed below, that the Examiner has not established a *prima facie* case for lack of utility for PRO1788 polypeptide.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.* According to the quoted statement, "WISP-1 gene amplification in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, a correlation between DNA amplification and over-expression of polypeptide **was observed** in the case of WISP-1.

Further, the Examiner cites the abstract of Konopka *et al.* to establish that "[p]rotein expression is not related to the amplification of the *abl* gene . . . ." Again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes in general. Konopka does not disclose any generalized teaching about the correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility

based on the results with the *abl* gene alone. Thus, the combined teachings of Pennica and Konopka are not directed towards genes in general but to single gene or genes within a family and thus, their teachings have been misinterpreted in this rejection.

Finally, the Examiner also cites the Haynes *et al.* reference to establish that "protein levels cannot be accurately predicted from the level of corresponding mRNA transcript." The Examiner adds that "Haynes *et al.* studied 80 proteins ... and found no strong correlation between proteins and transcript levels." Applicants respectfully traverse and point out that, on the contrary, Haynes teaches that "*there was a general trend* but no strong correlation between protein [expression] and transcript levels" (See page 1863, under Section 2.1, emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be *accurately* predicted from the level of the corresponding mRNA transcript" (See page 1863, under Section 2.1, last line, emphasis added). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst *most* of the 80 yeast proteins studied but the correlation is not linear, hence authors suggest that one cannot *accurately* predict protein levels from mRNA levels. In fact, very <u>few</u> data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, the Haynes data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants respectfully submit that the Examiner's rejection is based on a misrepresentation of the data presented in Haynes *et al.*

Accordingly, as stated above, since the standard is <u>not</u> absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance and the burden to provide further evidence of utility has not shifted to Applicants.

<u>It is "more likely than not" for amplified genes to have increased mRNA and protein levels</u>

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect

and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "... 62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers.

As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein

expressed from that mRNA.

While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, with the Examiner citing Pennica *et al.* (1998) and Konopka (1986), that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels.

Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1788 gene, that the PRO1788 protein is concomitantly overexpressed.

Accordingly, the presumption of specific, substantial and credible asserted utility stands, and the burden to provide further evidence of utility has not shifted to Applicants.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility. In support, Applicants particularly draw the Examiner's attention to page 2 of the Declaration by Dr. Ashkenazi which explains that,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. (Pathology Associates Medical Laboratores, August (1999), copy enclosed). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Therefore, Applicants respectfully submit that the gene amplification data provided in the present application, as discussed above, are sufficient to establish a specific, substantial and credible utility for the PRO1788 polypeptide, for example, to be used as a diagnostic marker of human colon cancer.

Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of Claims 28-35 and 38-40 under 35 U.S.C. §101.

4. **Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Enablement)**

Claims 28-40 are rejected under 35 U.S.C. 112, first paragraph allegedly because "the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Applicants disagree and respectfully traverse the rejection.

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot.

In response to the previous "lack of utility" rejection, Applicants have shown that the claimed polypeptides do have at least one patentable utility, namely utility in the diagnosis of colon tumor. Further, without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Claims 28-32 (and, as a consequence, those claims dependent from the same) have been amended to recite "wherein the nucleic acid encoding the polypeptide is amplified in colon tumors." In addition, applicants have established in response to the "lack of utility" rejection that more likely than not there is a correlation between the overexpression of the encoding nucleic acid and that of the encoded protein. Since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01.

In view of the discussions above regarding the utility of the polypeptides, Applicants submit that Claims 28-36 and 38-40 satisfy the enablement requirement because one skilled in the art would know how to make and use the claimed polypeptides in assays for the diagnosis of colon tumor. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 28-33, 36-37 and 39-40 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner asserts that "the claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, no other disclosed distinguishing feature."

Applicants disagree and respectfully traverse the rejection.

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot.

Without acquiescing to the propriety of this rejection, solely in the interest of expediting prosecution in this case, Applicants respectfully submit that amended Claims 28-32 (and, as a consequence, those claims dependent from the same) now recite a functional limitation that "the nucleic acid encoding the polypeptide is amplified in colon tumors." This biological activity, coupled with a well defined, and relatively high degree of sequence identity are believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. Hence, the present rejection should be withdrawn.

5. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 28-33, 36-37 & 39-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that "the polypeptide identified as PRO1788 is disclosed to possess two transmembrane domains in Figure 232, which would result in multiple extracellular domains. Therefore, it is unclear what is meant by the recitation of 'extracellular domain' in the current claims. Moreover, if the polypeptide possesses an extracellular domain, the recitation of 'the extracellular domain ... lacking its associated signal sequence' is indefinite (e.g., claims 28(d)

& 37), because a signal sequence is not generally considered to be part of an extracellular domain, in that signal sequences are cleaved from such domains during secretion from the cell."

Applicants disagree and respectfully traverse the rejection.

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot.

Since the terms "extracellular domain" and "extracellular domain lacking its associated signal peptide" is no longer present in Claims 28-33 (and, as a consequence, those claims dependent from the same), the rejection is believed to be moot, and should be withdrawn.

6. **Claim Rejections Under 35 U.S.C. § 102**

Claims 28-33, 36-37 & 39 are rejected under 35 U.S.C. 102(a) as being anticipated by Koehrer *et al.* (clone DKFZp586E011; Protein Sequence Database Accession No. T14791; August 1999).

According to the Examiner, "Koehrer *et al.* disclose a human polypeptide that is 99.6 % identical to residue #s 112-353 of SEQ ID NO: 397, which comprises the extracellular domain between residue # 305-353 of PRO1788 and/or comprises 100% sequence identity of the extracellular domain between residue # 233-286 of PRO1788, which further lacks the associated signal peptide of residue #s 1-16 (i.e., as it relates to claims 28 (c)&(d), 29 (c)&(d), 30 (c)&(d), 31 (c)&(d), 32(c)&(d), 33 (c)&(d), 36 & 37), and which comprises heterologous amino acid residues when compared to the putative extracellular regions of SEQ ID NO: 397 (i.e., as it relates to claim 39)."

Applicants disagree and respectfully traverse the rejection.

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot. Furthermore, as amended, Claims 28-33 (and, as a consequence, those claims dependent from the same) no longer recite terms "extracellular domain" and "extracellular domain lacking its associated signal peptide", thus Applicants submit that the cancellation of parts (c) and (d) in Claims 28-33 renders the rejection of these claims moot.

In addition, Applicants respectfully submit that SEQ ID NO:397 of the present application comprises 353 amino acids. However, Koehrer *et al.* disclose a polypeptide of only

242 residues having only about 68% sequence identity to the entire length of SEQ ID NO:397 of the present application. Therefore, Claims 28-33 (and, as a consequence, those claims dependent from the same) are not anticipated by Koehrer *et al.* Hence, Applicants respectfully submit that Koehrer *et al.* is not prior art under 102(a) and the Examiner is respectfully requested to withdraw the present rejection.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C42**).

Respectfully submitted,

Date: January 18, 2005

By: _____
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